CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-903

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

Division Director's Memorandum

NDA:	**20-903**
Drug and indication:	**ribavirin in combination with interferon alfa-2b (Rebetol™/Intron® A)**
Dose:	**600 mg twice daily/ 3 million units three times weekly**
Applicant:	**Schering-Plough Research Institute**
Submission dated:	**December 3, 1997**
Date of Memorandum:	**June 1, 1998**

In this application, the sponsor requests approval for oral ribavirin in combination with the licensed biologic product, interferon alfa-2b, for treatment of chronic hepatitis C infection in patients with compensated liver disease who have relapsed following alfa interferon monotherapy. The primary source of evidence supporting the safety and efficacy of this combination is the results of two randomized, placebo-controlled clinical trials, conducted in 345 male and female adult patients. Additional information on safety is provided by data from ongoing studies in other patient populations and by open-label experience. In both of the controlled trials, patients randomized to receive ribavirin in combination with interferon had a significantly higher rate of virologic response than did patients in the interferon monotherapy groups. Rates of histologic improvement were also higher in combination therapy recipients than in monotherapy recipients. However, the differences between treatments were less pronounced on the histologic endpoint than on the virologic endpoint.

The safety profile of interferon has been previously well-characterized. Additional serious safety issues raised by combination treatment with ribavirin include the frequent occurrence of hemolytic anemia (which has the potential for more serious complications in patients with cardiovascular disease) and the risk of teratogenicity. Safe use of this product will therefore require a commitment on the part of providers and patients to adhere to the labeled recommendations for close monitoring of clinical and laboratory parameters, and the need for effective contraception during and for six months after a course of therapy. To partially address the need for intensive patient education, a detailed patient package insert has been developed through collaboration with DDMAC.

I concur with the recommendation of the primary reviewers and with the consensus of the Antiviral Drugs Advisory Committee that this application be approved. Hepatitis C is a serious disease without adequate treatment options and the established risks of treatment appear to be appropriately balanced by the potential for clinical benefit, in patients similar to those enrolled in

the submitted trials. However, several questions about the use of this therapy remain unanswered by the information provided. Importantly, there is currently no information on whether short-term improvement (in virology and histology) predicts a reduction in risk for long-term serious sequelae (such as cirrhosis, hepatocellular cancer and death). Additionally, there is currently no information on the safety and efficacy of this therapy in other patient populations (including those with more advanced liver disease, patients coinfected with HIV, pediatric patients, liver transplant recipients, and patients without previous treatment experience). Because dose-finding studies were not conducted prior to initiation of these phase III studies, data is needed to address whether lower doses of ribavirin in combination with interferon might be similarly effective but safer. The applicant has committed to address these issues in phase IV by submitting data from ongoing studies or by conducting new investigations.

Because ribavirin is a known teratogen in animals and interferon has been shown to have abortifacent and other adverse animal reproductive effects, the sponsor has committed to establishment of a pregnancy registry to provide information to women who may have become pregnant during, or following treatment. This registry will also provide a mechanism for prospective monitoring of pregnancy outcomes in exposed women. Additionally, the need for effective contraception in male and female patients is prominently discussed in multiple sections of the package insert (including in a "black box" warning, in *Contraindications*, in *Precautions - Information for Patients*, *Precautions - Impairment of Fertility*, *Precautions - Pregnancy,* and *Dosage and Administration*).

Other phase IV commitments include: assessment of the effect of food on dosing; completion of new studies to assess animal carcinogenicity with ribavirin; development of packaging for patients who require a reduced ribavirin dose; and work to assess the relationship between virologic response and histologic improvement.

There are no outstanding regulatory issues.

/S/

Heidi M. Jolson, M.D., M.P.H.
Director, HFD-530

cc:
NDA20-903
HFD-530/Jolson/Fleischer/Crescenzi

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In accordance with section 306(k) of the Food, Drug and Cosmetic Act, Schering Corporation certifies that, with respect to this application, it did not and will not knowlingy use the services of any persons that have been debarred under the provisions of Section 306(a) or (b) of the Act.

APPEARS THIS WAY
ON ORIGINAL

In accordance with 21 CFR 314.50 (d)(1)(v), Schering Corporation certifies that a true copy of Section 4, Chemistry, Manufacturing and Control Information of this original NDA is being sent to FDA's New Jersey District Office.

APPEARS THIS WAY
ON ORIGINAL

Patent Information Pursuant to 21 CFR § 314.53

RE: COMBINED THERAPY OF INTRON ®A(INTERFERON ALFA-2b, RECOMBINANT)AND TRADENAME(RIBAVIRIN) TO TREAT CHRONIC HEPATITIS C VIRAL INFECTIONS IN INTERFERON RELAPSE PATIENTS

I.	A.	**Trade Name:**	INTRON ®A
		Active Ingredient:	Interferon alfa-2b, recombinant
		Strength:	3 million IU
		Dosage Form:	Solution for Injection
I.	B.	**Trade Name:**	TRADENAME
		Active Ingredient:	Ribavirin (1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide
		Strength:	200 mg
		Dosage Form:	Capsule

Pursuant to the provisions of 21 CFR § 314.53 we are hereby supplying the patent information for the captioned Schering Corporation ("Schering") NDA:

I.	A.	**U.S. Patent No.**	4,530,901
		Expiration Date:	July 23, 2002
		Type of Patent:	Recombinant DNA molecules and hosts transformed with such molecules which produce interferon alfa-2, recombinant,which is one of the active ingredients in the combined therapy for treating chronic hepatitis C viral infections for which approval is currently being sought.
		Patent Owner:	Biogen N.V.

II. B. U.S. Patent No. 4,211,771

Expiration Date: July 8, 1999

Type of Patent: Method of treating viral infections in viral diseases in humans using ribavirin, one of the active ingredients in the combined therapy for treating chronic hepatitis C viral infections for which approval is currently being sought.

Patent Owner: ICN

The undersigned declares (a) that the above-stated U.S. Patent No. 4,530,901 covers interferon-alfa-2b,recombinant, as a composition of matter per se, and (b) that interferon alfa-2b, recombinant is the active ingredient in INTRON A,which is an active ingredient in the combination therapy for treating chronic hepatitis C viral infections and (c) that the above-stated U.S. Patent No. 4,211,771 covers a method of using ribavirin to treat viral infections in mammals, and that (d) ribavirin is an active ingredient used in the combination therapy.

The undersigned further declares that approval for the combination therapy of INTRON A and ribavirin is being sought under Section 505 of The Federal Food, Drug and Cosmetic Act, 21 USC § 355 and that a claim of patent infringement under U.S. Patent 4,211,771 and 4,530,901 could reasonably be asserted if a person not licensed by the owners of each of the above-stated U.S. patents engaged in the manufacture, use or sale of Intron A or ribavirin for use in the combination therapy.

EXCLUSIVITY SUMMARY FOR NDA # 20-903

Trade Name **INTRON A/REBETOL** Generic Name **interferon alfa-2b, recombinant/ribavirin**
Applicant Name **Schering Corporation** HFD # **530**
Approval Date If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /__X__/ NO /__/

b) Is it an effectiveness supplement?

YES /__/ NO /__X__/

If yes, what type? (SE1, SE2, etc.)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no").

YES /__X__/ NO /__/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /_X_/ NO /__/

If the answer to (d) is "yes", how many years of exclusivity did the applicant request?

3 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES /__/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /__/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /__/ NO /__/

If "yes", identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one-never-before-approved active moiety and one previously approved active moiety, answer "yes". (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved).

YES / X / NO / ___ /

If "yes", identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ **Interferon alfa-2b, recombinant**

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES", GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant". This section should be completed only if the answer to PART II, Question 1 or 2 was "yes".

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies). If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes", then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /__/

IF "NO", GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /__/

If "no", state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X_/ NO /__/

(1) If the answer to 2(b) is "yes", do you personally know of any reason to disagree with the applicant's conclusion?

YES /__/ NO /_X_/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no", are you aware of published studies not conducted or sponsored by the applicant or other publicly available date that could independently demonstrate the safety and effectiveness of this drug product?

YES /__/ NO /__/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no", identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval", has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no").

Investigation #1 YES /__/ NO /_X_/

Investigation #2 YES /__/ NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /__/ NO /_X_/

Investigation #2 YES /__/ NO /_X_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are "no", identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

C95-144 _____

I95-145 _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES / X / NO /__/ Explain: _____

_____

Investigation #2

IND # _____ YES / X / NO /__/ Explain: _____

_____

b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /__/ Explain _____ NO /__/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /__/ Explain _____ NO /__/ Explain _____

_____ _____

_____ _____

(c) Not withstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest)

YES /__/ NO /_X_/

If yes, explain: _____

_____

/S/ 5/15/98

Signature of Project Manager — Date

/S/ 6/2/98

Signature of Division Director — Date

cc: Orig NDA Div File HFD-85

CLAIM for EXCLUSIVITY

1. Pursuant to the provisions of Sections 505 (c) (3) (D) (iii) and 505 (j) (4) (D) (iii) of the Food, Drug and Cosmetic Act and 21 CFR 314.108 (b) (4), the applicant claims three (3) years of exclusivity for its Combined Therapy of Intron A (Interferon alfa-2b, recombinant) and Tradename (Ribavirin)to treat chronic hepatitis C viral infection in interferon relapse patients.

2. The applicant certifies that to the best of the applicant's knowledge each of the clinical investigations included in the application meets the definition of "new clinical investigation" set forth in 21 CFR 314.108 (a).

3. A list of all published studies and publicly available reports of clinical investigations known to the applicant through a computer-assisted literature search that are relevant to the Combined Therapy for which the applicant is seeking approval is provided as **Attachment 1.**

4. The applicant certifies that it has thoroughly searched the scientific literature through a computer-assisted search of the ICON (Interferon Communication Network) database and the Dialog database encompassing the subfiles, MEDLINE, BIOSIS, EMBASE and SciSearch , for English and non-English literature relating to clinical studies of Combined Therapy of Intron A (Interferon alfa-2b, recombinant) and Tradename (Ribavirin) to treat chronic hepatitis C viral infection in interferon relapse patients during the period from11/5/87 to 11/5/97.

5. To the best of the applicant's knowledge, the list of scientific literature pertaining to INTRON A and Tradename (Ribavirin) is complete and accurate and, in the opinion of the applicant, the publicly available information does not provide a sufficient basis, without reference to the new clinical investigations in this application, for the approval of the Combined Therapy of Intron A (Interferon alfa-2b, recombinant) and Tradename (Ribavirin) to treat chronic hepatitis C viral infection in interferon relapse patients. The applicant's opinion that the studies or reports are insufficient is based on the following:

   - The literature does not contain adequate characterization of the safety and efficacy profiles of INTRON A and Tradename (Ribavirin) in this Combined Therapy, which are established by the data from the new clinical investigations conducted by the sponsor under [redacted] and are included in this application.

   - The overall clinical program requirements of this application, and the design of the studies were discussed with the Food and Drug Administration's Division of Antiviral Drug Products prior to study initiation. These studies were also reviewed by the Division during a June 30,1997 pre-NDA meeting. Such studies are not available in the published literature without reference to the sponsor's new clinical investigations.

6. The applicant was the sponsor named in the Form FDA-1571 for [redacted] under which the new clinical investigations were conducted.

Attachment 1

APPEARS THIS WAY
ON ORIGINAL

* Results of Clinical Investigation Included in NDA 20-903

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-903 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-530 Trade and generic names/dosage form: Intron A (interferon alfa-2b recombinant) injection /Rebetol (ribavirin) capsules Action: AP AE NA

Applicant Schering Corporation Therapeutic Class 7030170 Antiviral/Systemic/Hepatitis

Indication(s) previously approved N/A

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate X

Indication in this application Treatment of chronic hepatitis C in patients 18 years of age or older with compensated liver disease who have relapsed following alfa interferon therapy. (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

X 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- X (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

[signature] Regulatory Management Officer 5/28/98

Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # 20-903
Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)